Figure 1

GAGCCCCGCATCCCGCCGCAGCTGCCGCCTCGCCGCGGCCGGGCCGGAGAGCACGGCGGCGGGAGCGCGGCCTTAGGAGG
CGGCCGGAGCGGTGGGCACAGCTCGGCGCGGAGCGTCCTGTCAGGCGGCGGCCGAGGGCGTCGCGGACTCTCCCCGCGAT
GATGCCGATGATATTAACTGTTTTCTTGAGCAACAATGAACAGATTTTAACAGAAGTTCCTATAACACCGGAAACAACCT
GTCGAGATGTTGTAGAATTTTGCAAGGAACCTGGAGAAGGCAGCTGCCATTTAGCTGAAGTGTGGAGGGGAAATGAACGT
CCCATACCCTTTGATCATATGATGTACGAACATCTTCAGATATGGGGTCCACGGAGGGAAGAAGTGAAATTTTTCCTTCG
ACACGAGGACTCCCCAACTGAGAACAGTGAACAAGGTGGCCGTCAGACCCAAGAGCAACGAACTCAGAGAAATGTAATAA
ATGTACCTGGAGATAAACGTACTGAATATGGGGTTGGGAATCCACGTGTTGAACTTACCCTCTCAGAGCTCCAAGATATG
GCAGCTAGGCAACAGCAGCAGATTGAAAATCAGCAGCAGATGTTGGTTGCCAAGGAACAGCGTTTACATTTTCTAAAGCA
ACAGGAGCGCCGTCAGCAGCAGTCTATTTCTGAAAATGAAAAGCTTCAGAAATTGAAAGAACGAGTTGAAGCCCAGGAGA
ACAAGCTGAAGAAAATTCGTGCAATGAGAGGACAAGTCGACTACAGCAAAATCATGAACGGCAATCTGTCTGCTGAAATA
GAAAGGTTCAGTGCCATGTTCCAGGAAAAGAAGCAGGAAGTACAGACTGCAATTTTAAGGGTTGATCAGCTTAGTCAGCA
ATTGGAAGATTTAAAGAAAGGAAAACTGAATGGGTTCCAGTCTTACAATGGCAAATTGACGGGACCAGCGGCGGTGGAGT
TAAAAAGACTGTACCAAGAACTACAGATTCGTAACCAACTTAACCAGGAACAAAATTCAAAACTTCAGCAGCAGAAGGAA
CTCTTAAATAAGCGCAACATGGAGGTGGCCATGATGGACAAGCGAATCAGTGAACTGCGTGAACGTCTCTATGGGAAAAA
AATTCAGCTGAACCGTGTGAATGGCACGTCATCACCACAGTCCCCTCTGAGCACATCGGGCAGGGTCGCTGCTGTGGGGC
CTTATATCCAGGTTCCCAGTGCCGGAAGCTTTCCTGTGCTGGGGGACCCTATAAAGCCCCAGTCTCTCAGTATTGCCTCA
AATGCTGCTCATGGAAGATCCAAATCCGCTAATGATGGAAACTGGCCAACATTAAAACAGAATTCTAGCTCTTCCGTGAA
ACCAGTGCAGGTGGCCGGTGCAGACTGGAAGGATCCGAGCGTGGAGGGGTCTGTCAAGCAGGGCACTGTCTCCAGCCAGC
CTGTGCCCTTCTCAGCACTGGGACCCACGGAGAAGCCGGGCATCGAGATTGGTAAAGTGCCACCTCCCATCCCGGGTGTA
GGCAAGCAGCTGCCTCCAAGCTATGGGACATACCCAAGTCCTACACCTCTGGGTCCTGGGTCGACAAGCTCCCTGGAAAG
GAGGAAGGAAGGCAGCTTGCCCAGGCCCAGTGCAGGCCTGCCAAGTCGACAGAGGCCCACCCTGCTGCCCGCCACAGGCA
GCACCCCCCAGCCAGGCTCCTCACAACAGATTCAGCAGAGGATTTCCGTACCGCCAAGTCCCACGTACCCGCCAGCGGGA
CCACCTGCATTTCCAGCTGGGGACAGCAAGCCTGAACTCCCACTGACAGTGGCCATTAGGCCTTTCCTGGCTGATAAAGG
GTCAAGGCCACAGTCTCCCAGGAAAGGACCCCAGACAGTGAATTCAAGTTCCATATACTCCATGTACCTCCAGCAAGCCA
CACCACCTAAGAATTACCAGCCGGCAGCACACAGCGCCTTAAATAAGTCAGTTAAAGCAGTGTATGGTAAGCCCGTTTTA
CCTTCGGGTTCAACCTCTCCATCGCCGCTGCCGTTTCTTCACGGGTCACTGTCCACGGGCACACCACAGCCTCAGCCACC
TTCAGAAAGTACTGAGAAAGAGCCTGAGCAGGATGGCCCCGCCGCCCCCGCAGATGGCAGCACCGTGGAGAGCCTGCCAC
GGCCACTCAGCCCCACCAAGCTCACGCCCATCGTGCATTCGCCACTGCGCTACCAGAGTGATGCAGACCTGGAGGCCCTC
CGCAGGAAGCTGGCCAACGCGCCCCGGCCCCTGAAAAAGCGCAGCTCCATCACAGAGCCCGAGGGCCCCGGCGGGCCCAA
CATCCAGAAGCTGCTGTACCAGCGCTTCAACACCCTGGCCGGTGGCATGGAGGGCACCCCTTTCTACCAGCCCAGCCCCT
CCCAGGACTTCATGGGCACCTTGGCCGATGTGGACAATGGAAACACCAATGCCAATGGAAACCTGGAAGAGCTCCCCCCT
GCCCAGCCCACAGCCCCACTCCCCGCTGAGCCTGCCCCGTCATCAGATGCCAATGATAATGAGTTACCTTCCCCCGAACC
AGAGGAGCTCATCTGTCCCCAAACCACCCACCAAACTGCCGAGCCGGCAGAGGACAATAACAACAACGTGGCCACGGTCC
CCACCACGGAGCAGATCCCGAGTCCTGTGGCTGAGGCCCCATCTCCAGGGGAAGAGCAGGTCCCTCCAGCACCTCTTCCC
CCTGCCAGCCACCCTCCTGCCACCTCCACGAACAAGCGGACCAACTTGAAGAAGCCCAACTCGGAGCGGACGGGGCACGG
GCTGAGAGTCCGGTTTAACCCCCTGGCACTGCTCCTAGACGCGTCTCTGGAAGGAGAGTTCGATCTGGTGCAGAGGATCA
TCTATGAGGTGGAAGATCCCAGCAAGCCCAACGATGAAGGGATCACCCCACTGCACAACGCCGTCTGCGCCGGCCACCAT
CACATCGTGAAGTTCCTGCTGGATTTTGGTGTCAACGTGAATGCTGCTGATAGTGATGGATGGACGCCGCTGCACTGCGC
TGCCTCTTGTAACAGCGTTCACCTCTGCAAACAGCTGGTGGAGAGTGGTGCCGCCATTTTTGCCTCAACCATAAGCGACA
TTGAAACTGCTGCAGACAAGTGTGAGGAGATGGAGGAAGGCTACATCCAGTGCTCCCAGTTTCTATATGGGGTGCAGGAA
AAGCTGGGTGTGATGAACAAAGGTGTGGCGTATGCTCTGTGGGACTACGAGGCCCAGAACAGTGACGAGCTGTCCTTCCA
CGAAGGGGACGCCCTCACCATCCTGAGGCGCAAGGACGAAAGCGAGACTGAGTGGTGGTGGGCTCGCCTTGGAGACCGGG
AGGGCTATGTGCCCAAAAACCTGCTGGGGCTGTATCCACGGATCAAACCCCGACAGCGAACACTCGCCTGAACTTCCTTT
TGGAGCACCGCATGGTCTTGCCAGCTACCAGGAGCCACTTAAGAGATTATTGTGCTGTTTTCCAGGAAAGCTGCAGCTAG
AAAATGGTCTTAATGGTGCTCACTTTAGCAGACAGCGTCCACAATGTGAATCCTACAGTTTCCAGGTGAGGCCCTTTCTC
CAGTTTGCCCATTAACTGGGAGAGGTACTTTCGCCTCCAAGGACTGAATTTTGCCAATTACTATAAATCCAAATAAATAC
CCACTTTCAAAACACCCACCCCTCTTGCCATTAAGAAGTCCCATAACCCCCGGTTGGTTGCCAGTGAAGACAGAAGCTCT
TACTGACTTGGCCCCGAGGCCATCACCCCCTCCAGCAGTGAACACTGTCCGCCGCTGTGAGGCCTGCTCCCCTGCGACCG
CCCTGCCCCCCGTCACCGAATCGGACACTCATCCTTTCTCACACTTCCCACACATGATCCTTCTTCCCTTCATCACCAAA
GGAGCCTCTGTATGGAAACATGTCCAGTGTTGCTGCCCAGTGTGTATGCCTCCCAGTACCCACTCTGCTCGGCCGCCTTG
GGGGTTCCGCTTCCTGTTCCAGTTCACCTAAAGGCTGATTGTGCAGGCCCAGCACTGTGGCTGGACTGCCGCGCCACGGG
CACCAGGACCCCTAAGACCAAGTGACAACTGGGAGAGCCTCAGCATATACTCTTCTCCTCCGATCTCACAGCCTGTCATG
CTGCTCAGTGTGGTTCTCACCCCTGCAAGCTCAAATTCAGTTCCCTGAATGGAGTCAGGTGCTGGAGGCCGTGGCAGCGG
AGGGTGGTTGGGGTTGGGGCTGGGGGTGGACTGGTGTGAGGGCAGACCAGGGCCAGGTAGACGGGGCTGTTTGGTGCCTG
AAGGATGGCAGACGCCTGGTGTCAGGAGGGGCCGCCACCAAGGAGCAGCAGCTGGGGCAGAGGAGCTGGGGTCAGGGGCC
ACCCCTCTCTGCCGATCTCCCTGCCTGGGCTGGCTGTGAGGCCACCTTTGTCCCAGGCCCAGCCTCAAGGCAAGGAGGGC
GCTTCACTGAGGTGTGAATTGTACGTACAGGCTTTTTATATACCAAAAGTATTTTTTGACTAGACCATTCAAAGCTACCC
GAACTATGTTGGAAATTTTTTTTTTTCTCATTAAAATACAGGCCCTTAGGCTCTATTTTTCATGTATGAGTCGTGTGTAA
TTTATGTAAAAATGTGTGTACAGACTCACTGATGCAGCACTGTAGCCCATCACCTTGGAGCACTGACTGTACATAGTGTG
GTGAAGAAAAGTGAACGCCCTTGTAGAGCAGCCCGACCACAGGAGCATGGCCGCTGCCAGCCCAGACGCTGCTGACGCTG
TGTAAATGTGCACAATAAACCCGTCTCACCCCGG

Figure 2

GTCACGAGCGTCGAAGAGACAAAGCCGCGTCAGGGGGCCCGGCCGGGGCGGGGGAGCCCGGGGCTTGTTGGTGCCCCAGC
CCGCGCGGAGGGCCCTTCGGACCCGCGCGCCGCCGCTGCCGCCGCCGCCGCCTCGCAACAGGTCCGGGCGGCCTCGCTCT
CCGCTCCCCTCCCCCGCATCCGCGACCCTCCGGGGCACCTCAGCTCGGCCGGGGCCGCAGTCTGGCCACCCGCTTCCATG
CGGTTCGGGTCCAAGATGATGCCGATGTTTCTTACCGTGTATCTCAGTAACAATGAGCAGCACTTCACAGAAGTTCCAGT
TACTCCAGAAACAATATGCAGAGACGTGGTGGATCTGTGCAAAGAACCCGGCGAGAGTGATTGCCATTTGGCTGAAGTGT
GGTGTGGCTCTGAACGTCCAGTTGCGGATAATGAGCGAATGTTTGATGTTCTTCAACGATTTGGAAGTCAGAGGAACGAA
GTTCGCTTCTTCCTTCGTCATGAACGCCCCCCTGGCAGGGACATTGTGAGTGGACCAAGATCTCAGGATCCAAGTTTAAA
AAGAAATGGTGTAAAAGTTCCTGGTGAATATCGAAGAAAGGAGAACGGTGTTAATAGTCCTAGGATGGATCTGACTCTTG
CTGAACTTCAGGAAATGGCATCTCGCCAGCAGCAACAGATTGAAGCCCAGCAACAATTGCTGGCAACTAAGGAACAGCGC
TTAAAGTTTTTGAAACAACAAGATCAGCGACAACAGCAACAAGTTGCTGAGCAGGAGAAACTTAAAAGGCTAAAAGAAAT
AGCTGAGAATCAGGAAGCTAAGCTAAAAAAAGTGAGAGCACTTAAAGGCCACGTGGAACAGAAGAGACTAAGCAATGGGA
AACTTGTGGAGGAAATTGAACAGATGAATAATTTGTTCCAGCAAAAACAGAGGGAGCTCGTCCTGGCTGTGTCAAAAGTA
GAAGAACTGACCAGGCAGCTAGAGATGCTCAAGAACGGCAGGATCGACAGCCACCATGACAATCAGTCTGCAGTGGCTGA
GCTTGATCGCCTCTATAAGGAGCTGCAGCTAAGAAACAAATTGAATCAAGAGCAGAATGCCAAGCTACAACAACAGAGGG
AGTGTTTGAATAAGCGTAATTCAGAAGTGGCAGTCATGGATAAGCGTGTTAATGAGCTGAGGGACCGGCTGTGGAAGAAG
AAGGCAGCTCTACAGCAAAAAGAAAATCTACCAGTTTCATCTGATGGAAATCTTCCCCAGCAAGCCGCGTCAGCCCCAAG
CCGTGTGGCTGCAGTAGGTCCCTATATCCAGTCGTCTACTATGCCTCGGATGCCCTCAAGGCCTGAATTGCTGGTGAAGC
CAGCCCTGCCGGATGGTTCCTTGGTCATTCAGGCTTCAGAGGGGCCGATGAAAATACAGACACTGCCCAACATGAGATCT
GGGGCTGCTTCACAAACTAAAGGCTCTAAAATCCATCCAGTTGGCCCTGATTGGAGTCCTTCAAATGCAGATCTTTTCCC
AAGCCAAGGCTCTGCTTCTGTACCTCAAAGCACTGGGAATGCTCTGGATCAAGTTGATGATGGAGAGGTTCCGCTGAGGG
AGAAAGAGAAGAAAGTGCGTCCGTTCTCAATGTTTGATGCAGTAGACCAGTCCAATGCCCCACCTTCCTTTGGTACTCTG
AGGAAGAACCAGAGCAGTGAAGATATCTTGCGGGATGCTCAGGTTGCAAATAAAAATGTGGCTAAAGTACCACCTCCTGT
TCCTACAAAACCAAAACAGATTAATTTGCCTTATTTTGGACAAACTAATCAGCCACCTTCAGACATTAAGCCAGACGGAA
GTTCTCAGCAGTTGTCAACAGTTGTTCCGTCCATGGGAACTAAACCAAAACCAGCAGGGCAGCAGCCGAGAGTGCTGCTA
TCTCCCAGCATACCTTCGGTTGGCCAAGACCAGACCCTTTCTCCAGGTTCTAAGCAAGAAAGTCCACCTGCTGCTGCCGT
CCGGCCCTTTACTCCCCAGCCTTCCAAAGACACCTTACTTCCACCCTTCAGAAAACCCCAGACCGTGGCAGCAAGTTCAA
TATATTCCATGTATACGCAACAGCAGGCGCCAGGAAAAAACTTCCAGCAGGCTGTGCAGAGCGCGTTGACCAAGACTCAT
ACCAGAGGGCCACACTTTTCAAGTGTATATGGTAAGCCTGTAATTGCTGCTGCCCAGAATCAACAGCAGCACCCAGAGAA
CATTTATTCCAATAGCCAGGGCAAGCCTGGCAGTCCAGAACCTGAAACAGAGCCTGTTTCTTCAGTTCAGGAGAACCATG
AAAACGAAAGAATTCCTCGGCCACTCAGCCCAACTAAATTACTGCCTTTCTTATCTAATCCTTACCGAAACCAGAGTGAT
GCTGACCTAGAAGCCTTACGAAAGAAACTGTCTAACGCACCAAGGCCTCTAAAGAAACGTAGTTCTATTACAGAGCCAGA
GGGTCCTAATGGGCCAAATATTCAGAAGCTTTTATATCAGAGGACCACCATAGCGGCCATGGAGACCATCTCTGTCCCAT
CATACCCATCCAAGTCAGCTTCTGTGACTGCCAGCTCAGAAAGCCCAGTAGAAATCCAGAATCCATATTTACATGTGGAG
CCCGAAAAGGAGGTGGTCTCTCTGGTTCCTGAATCATTGTCCCCAGAGGATGTGGGGAATGCCAGTACAGAGAACAGTGA
CATGCCAGCTCCTTCTCCAGGCCTTGATTATGAGCCTGAGGGAGTCCCAGACAACAGCCCAAATCTCCAGAATAACCCAG
AAGAACCAAATCCAGAGGCTCCACATGTGCTTGATGTGTACCTGGAGGAGTACCCTCCATACCCACCCCCACCATACCCA
TCTGGGGAGCCTGAAGGGCCCGGAGAAGACTCGGTGAGCATGCGCCCGCCTGAAATCACCGGGCAGGTCTCTCTGCCTCC
TGGTAAAAGGACAAACTTGCGTAAAACTGGCTCAGAGCGTATCGCTCATGGAATGAGGGTGAAATTCAACCCCCTTGCTT
TACTGCTAGATTCGTCTTTGGAGGGAGAATTTGACCTTGTACAGAGAATTATTTATGAGGTTGATGACCCAAGCCTCCCC
AATGATGAAGGCATCACGGCTCTTCACAATGCTGTGTGTGCAGGCCACACAGAAATCGTTAAGTTCCTGGTACAGTTTGG
TGTAAATGTAAATGCTGCTGATAGTGATGGATGGACTCCATTACATTGTGCTGCCTCATGTAACAACGTCCAAGTGTGTA
AGTTTTTGGTGGAGTCAGGAGCCGCTGTGTTTGCCATGACCTACAGTGACATGCAGACTGCTGCAGATAAGTGCGAGGAA
ATGGAGGAAGGCTACACTCAGTGCTCCCAATTTCTTTATGGAGTTCAGGAGAAGATGGGCATAATGAATAAAGGAGTCAT
TTATGCGCTTTGGGATTATGAACCTCAGAATGATGATGAGCTGCCCATGAAAGAAGGAGACTGCATGACAATCATCCACA
GGGAAGACGAAGATGAAATCGAATGGTGGTGGGCGCGCCTTAATGATAAGGAGGGATATGTTCCACGTAACTTGCTGGGA
CTGTACCCAAGAATTAAACCAAGACAAAGGAGCTTGGCCTGAAACTTCCACACAGAATTTTAGTCAATGAAGAATTAATC
TCTGTTAAGAAGAAGTAATACGATTATTTTTGGCAAAAATTTCACAAGACTTATTTTAATGACAATGTAGCTTGAAAGCG
ATGAAGAATGTCTCTAGAAGAGAATGAAGGATTGAAGAATTCACCATTAGAGGACATTTAGCGTGATGAAATAAAGCATC
TACGTCAGCAGGCCATACTGTGTTGGGGCAAAGGTGTCCCGTGTAGCACTCAGATAAGTATACAGCGACAATCCTGTTTT
CTACAAGAATCCTGTCTAGTAAATAGGATCATTTATTGGGCAGTTGGGAAATCAGCTCTCTGTCCTGTTGAGTGTTTTCA
GCAGCTGCTCCTAAACCAGTCCTCCTGCCAGAAAGGACCAGTGCCGTCACATCGCTGTCTCTGATTGTCCCCGGCACCAG
CAGGCCTTGGGGCTCACTGAAGGCTCGAAGGCACTGCACACCTTGTATATTGTCAGTGAAGAACGTTAGTTGGTTGTCAG
TGAACAATAACTTTATTATATGAGTTTTTGTAGCATCTTAAGAATTATACATATGTTTGAAATATTGAAACTAAGCTACA
GTACCAGTAATTAGATGTAGAATCTTGTTTGTAGGCTGAATTTTAATCTGTATTTATTGTCTTTTGTATCTCAGAAATTA
GAAACTTGCTACAGACTTACCCGTAATATTTGTCAAGATCATAGCTGACTTTAAAAACAGTTGTAATAAACTTTTTGATG
CT

Figure 3

MMPMILTVFLSNNEQILTEVPITPETTCRDVVEFCKEPGEGSCHLAEVWRGNERPIPFDHMMYEHLQIWGPRREEVKFFL
RHEDSPTENSEQGGRQTQEQRTQRNVINVPGDKRTEYGVGNPRVELTLSELQDMAARQQQQIENQQQMLVAKEQRLHFLK
QQERRQQQSISENEKLQKLKERVEAQENKLKKIRAMRGQVDYSKIMNGNLSAEIERFSAMFQEKKQEVQTAILRVDQLSQ
QLEDLKKGKLNGFQSYNGKLTGPAAVELKRLYQELQIRNQLNQEQNSKLQQQKELLNKRNMEVAMMDKRISELRERLYGK
KIQLNRVNGTSSPQSPLSTSGRVAAVGPYIQVPSAGSFPVLGDPIKPQSLSIASNAAHGRSKSANDGNWPTLKQNSSSSV
KPVQVAGADWKDPSVEGSVKQGTVSSQPVPFSALGPTEKPGIEIGKVPPPIPGVGKQLPPSYGTYPSPTPLGPGSTSSLE
RRKEGSLPRPSAGLPSRQRPTLLPATGSTPQPGSSQQIQQRISVPPSPTYPPAGPPAFPAGDSKPELPLTVAIRPFLADK
GSRPQSPRKGPQTVNSSSIYSMYLQQATPPKNYQPAAHSALNKSVKAVYGKPVLPSGSTSPSPLPFLHGSLSTGTPQPQP
PSESTEKEPEQDGPAAPADGSTVESLPRPLSPTKLTPIVHSPLRYQSDADLEALRRKLANAPRPLKKRSSITEPEGPGGP
NIQKLLYQRFNTLAGGMEGTPFYQPSPSQDFMGTLADVDNGNTNANGNLEELPPAQPTAPLPAEPAPSSDANDNELPSPE
PEELICPQTTHQTAEPAEDNNNNVATVPTTEQIPSPVAEAPSPGEEQVPPAPLPPASHPPATSTNKRTNLKKPNSERTGH
GLRVRFNPLALLLDASLEGEFDLVQRIIYEVEDPSKPNDEGITPLHNAVCAGHHHIVKFLLDFGVNVNAADSDGWTPLHC
AASCNSVHLCKQLVESGAAIFASTISDIETAADKCEEMEEGYIQCSQFLYGVQEKLGVMNKGVAYALWDYEAQNSDELSF
HEGDALTILRRKDESETEWWWARLGDREGYVPKNLLGLYPRIKPRQRTLA

Figure 4

MMPMFLTVYLSNNEQHFTEVPVTPETICRDVVDLCKEPGESDCHLAEVWCGSERPVADNERMFDVLQRFGSQRNEVRFFL
RHERPPGRDIVSGPRSQDPSLKRNGVKVPGEYRRKENGVNSPRMDLTLAELQEMASRQQQQIEAQQQLLATKEQRLKFLK
QQDQRQQQQVAEQEKLKRLKEIAENQEAKLKKVRALKGHVEQKRLSNGKLVEEIEQMNNLFQQKQRELVLAVSKVEELTR
QLEMLKNGRIDSHHDNQSAVAELDRLYKELQLRNKLNQEQNAKLQQQRECLNKRNSEVAVMDKRVNELRDRLWKKKAALQ
QKENLPVSSDGNLPQQAASAPSRVAAVGPYIQSSTMPRMPSRPELLVKPALPDGSLVIQASEGPMKIQTLPNMRSGAASQ
TKGSKIHPVGPDWSPSNADLFPSQGSASVPQSTGNALDQVDDGEVPLREKEKKVRPFSMFDAVDQSNAPPSFGTLRKNQS
SEDILRDAQVANKNVAKVPPPVPTKPKQINLPYFGQTNQPPSDIKPDGSSQQLSTVVPSMGTKPKPAGQQPRVLLSPSIP
SVGQDQTLSPGSKQESPPAAAVRPFTPQPSKDTLLPPFRKPQTVAASSIYSMYTQQQAPGKNFQQAVQSALTKTHTRGPH
FSSVYGKPVIAAAQNQQQHPENIYSNSQGKPGSPEPETEPVSSVQENHENERIPRPLSPTKLLPFLSNPYRNQSDADLEA
LRKKLSNAPRPLKKRSSITEPEGPNGPNIQKLLYQRTTIAAMETISVPSYPSKSASVTASSESPVEIQNPYLHVEPEKEV
VSLVPESLSPEDVGNASTENSDMPAPSPGLDYEPEGVPDNSPNLQNNPEEPNPEAPHVLDVYLEEYPPYPPPPYPSGEPE
GPGEDSVSMRPPEITGQVSLPPGKRTNLRKTGSERIAHGMRVKFNPLALLLDSSLEGEFDLVQRIIYEVDDPSLPNDEGI
TALHNAVCAGHTEIVKFLVQFGVNVNAADSDGWTPLHCAASCNNVQVCKFLVESGAAVFAMTYSDMQTAADKCEEMEEGY
TQCSQFLYGVQEKMGIMNKGVIYALWDYEPQNDDELPMKEGDCMTIIHREDEDEIEWWWARLNDKEGYVPRNLLGLYPRI
KPRQRSLA

Figure 5

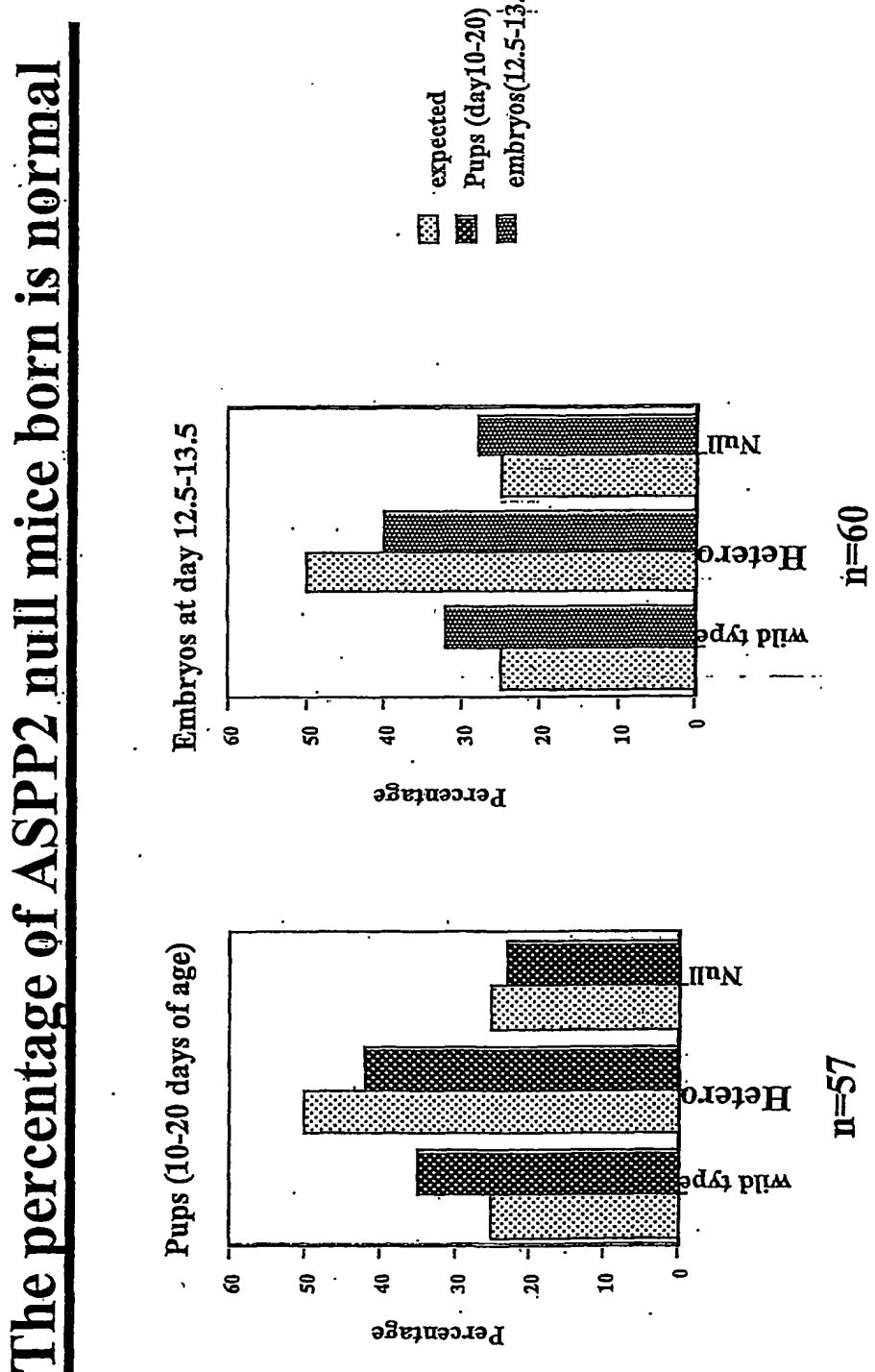

The percentage of ASPP2 null mice born is normal
expected
Pups (day10-20)
embryos(12.5-13.5)
Embryos at day 12.5-13.5
Percentage
60
50
40
30
20
10
0
wild type
Hetero
Null
n=60
Pups (10-20 days of age)
Percentage
60
50
40
30
20
10
0
wild type
Hetero
Null
n=57

Figure 6

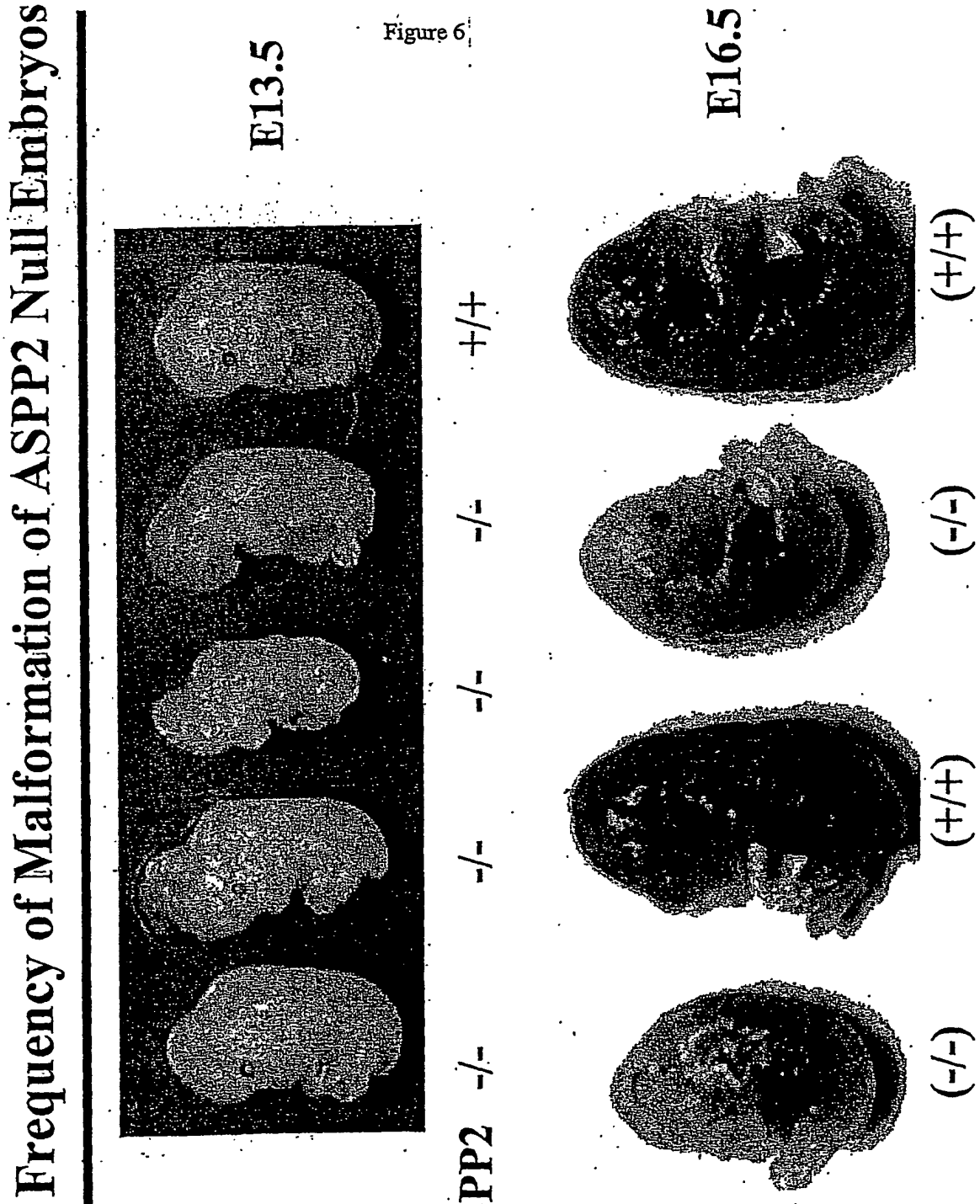

High Frequency of Malformation of ASPP2 Null Embryos
E13.5
E16.5
ASPP2 -/- -/- -/- +/+
(-/-) (+/+) (-/-) (+/+)

Figure 7

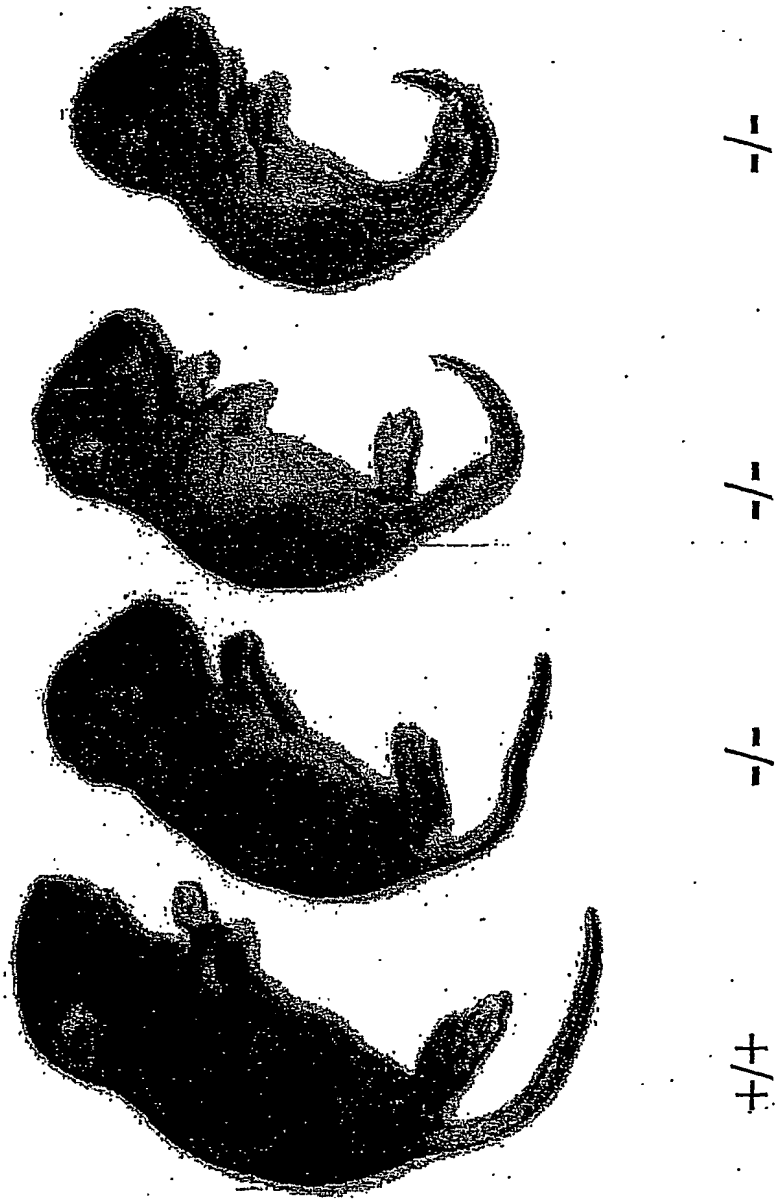


Figure 8

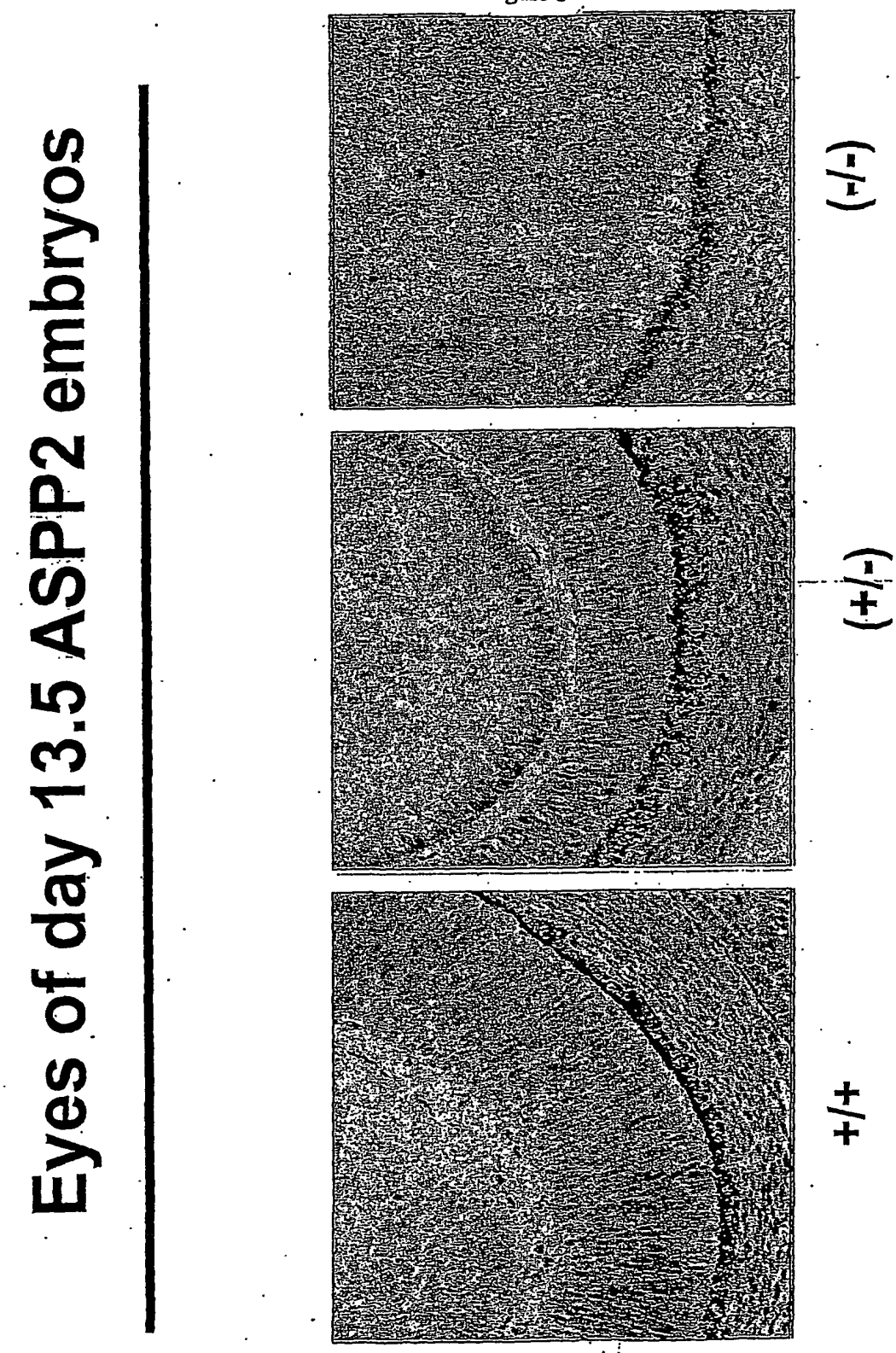


Figure 9

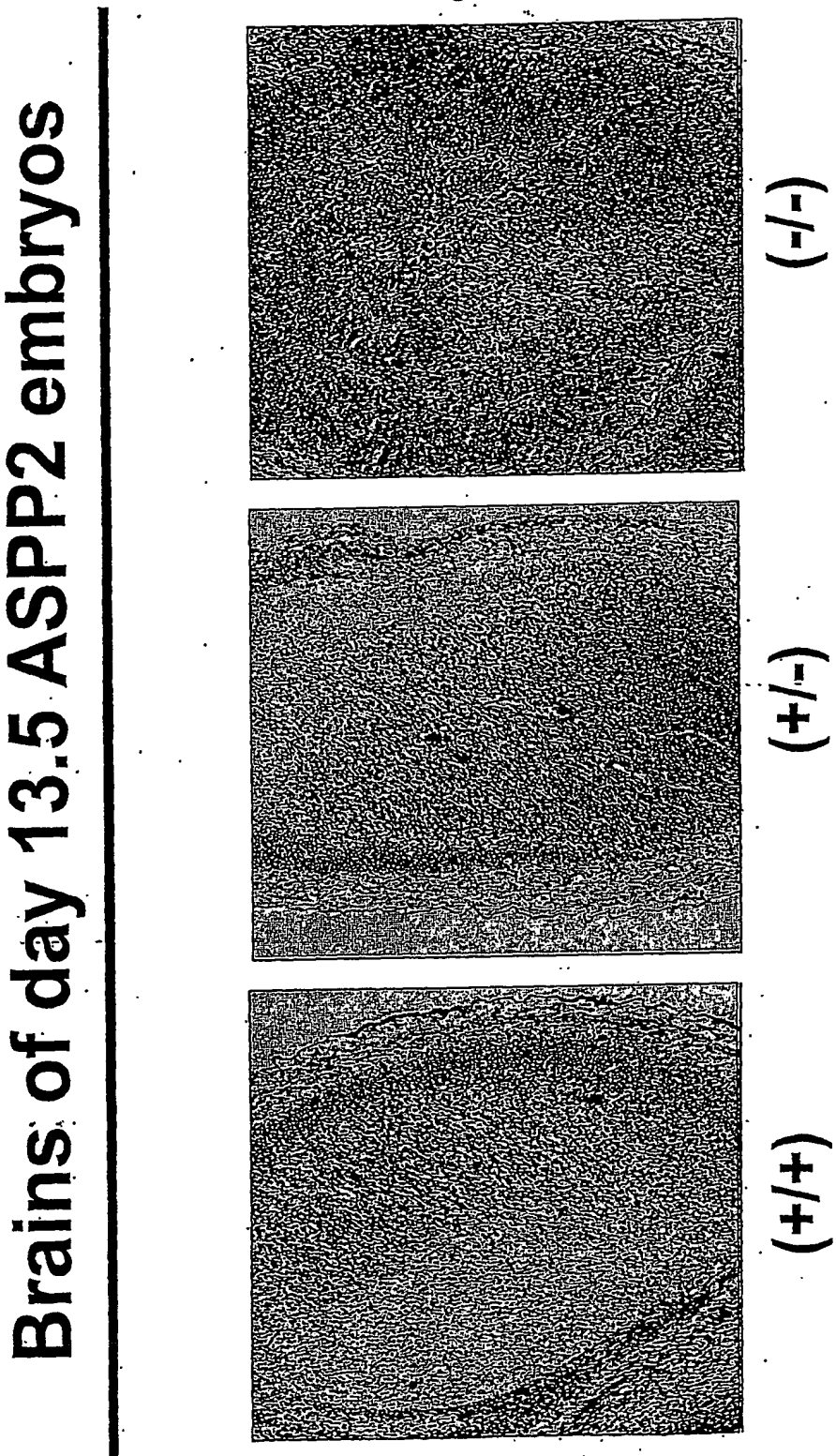


Figure 10

Abnormal growth in the brain of ASPP2 null embryo

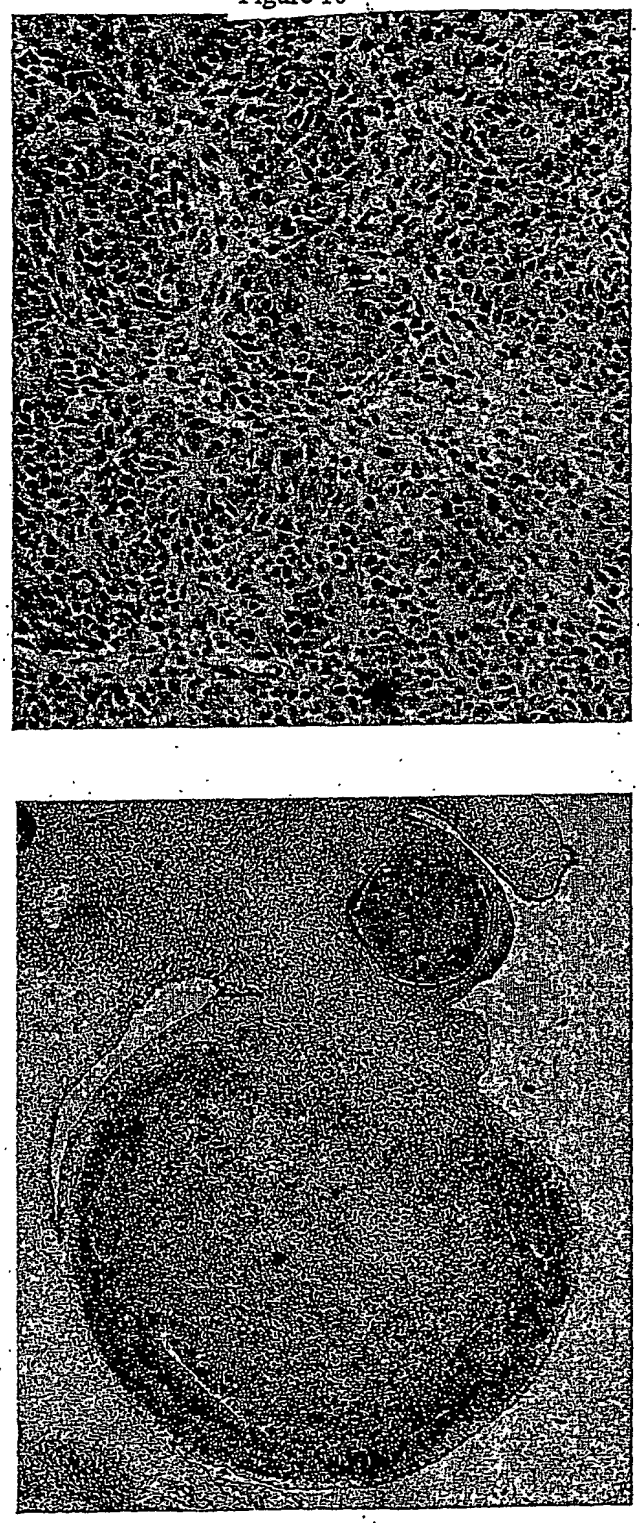
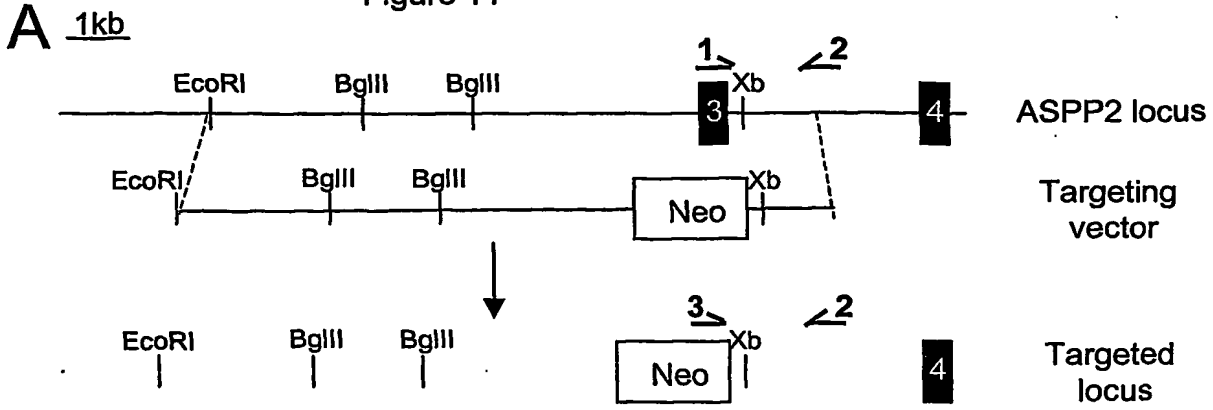
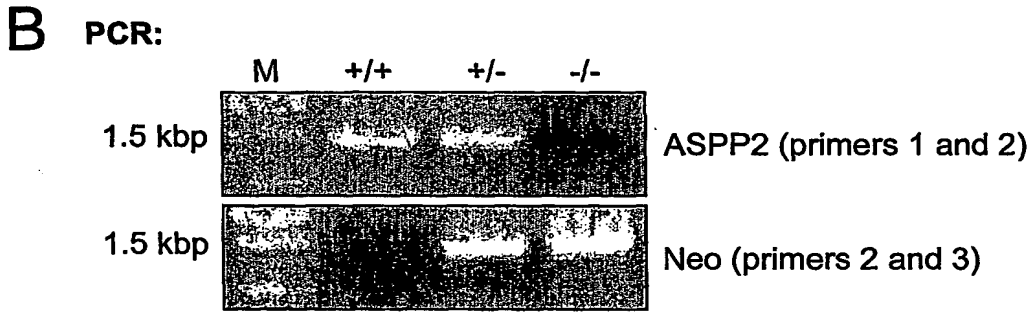
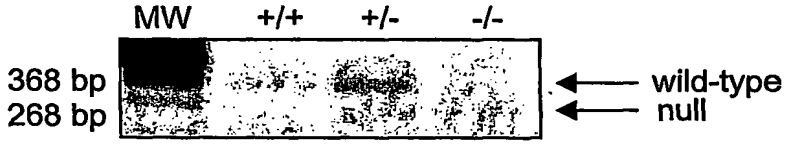


Figure 11


A
1kb
EcoRI
BglII
BglII
1
2
Xb
3
4
ASPP2 locus
EcoRI
BglII
BglII
Neo
Xb
Targeting vector
EcoRI
BglII
BglII
3
2
Xb
Neo
4
Targeted locus


B PCR:
M
+/+
+/-
-/-
1.5 kbp
ASPP2 (primers 1 and 2)
1.5 kbp
Neo (primers 2 and 3)


C RT-PCR:
MW
+/+
+/-
-/-
368 bp
268 bp
wild-type
null

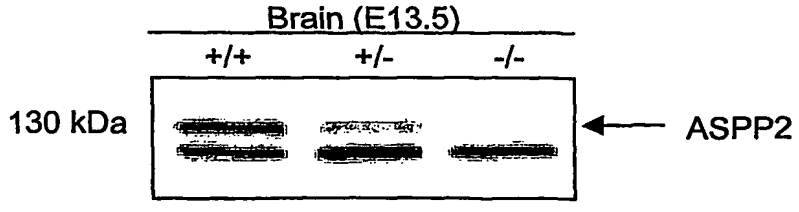
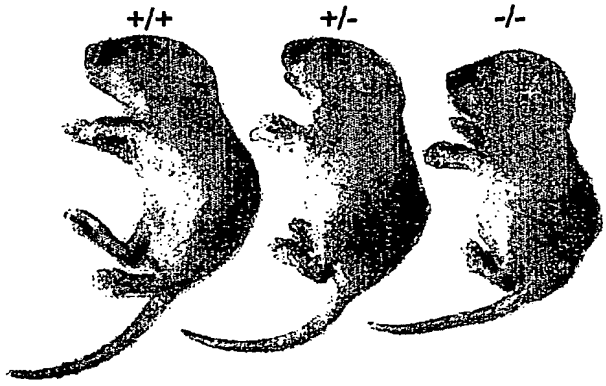
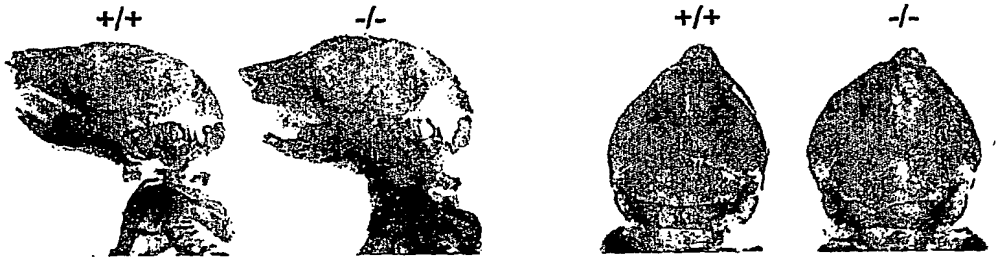

D Western Blot:
Brain (E13.5)
+/+
+/-
-/-
130 kDa
ASPP2

Figure 12

A **P9 pups phenotype:**

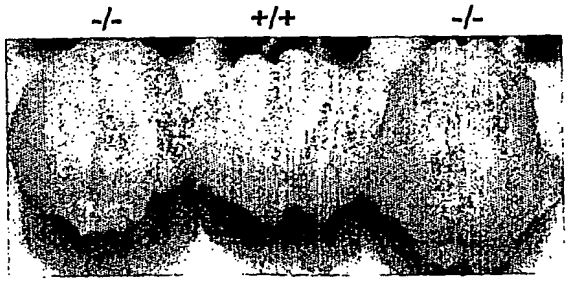


B **P24 skulls staining (Alizarin red - Alcian blue):**



profile view dorsal view

C **Gross morphology of P5 brains:**



ASPP2+/+ Figure 13 ASPP2 -/-

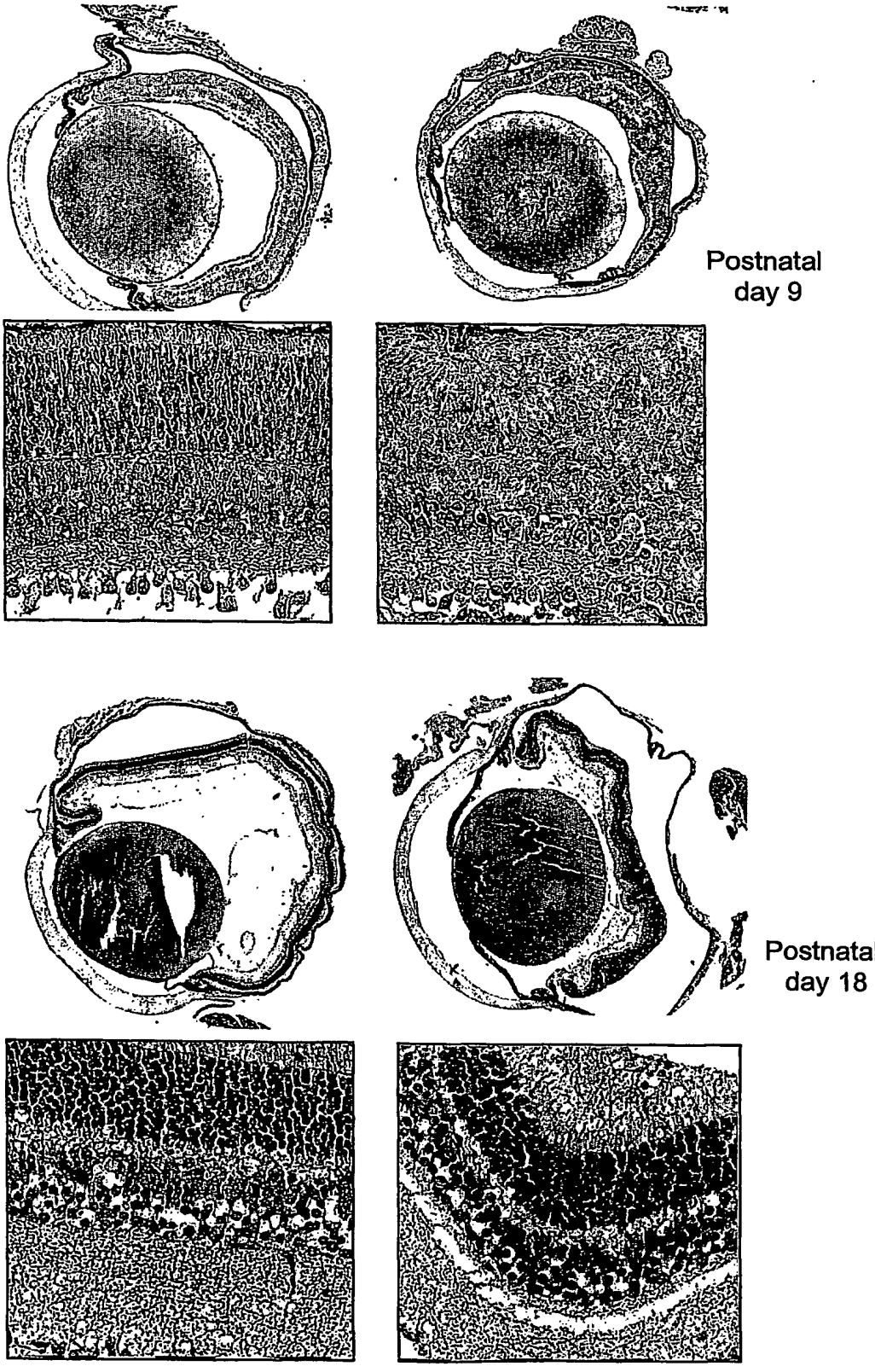


Figure 14

D11.5 embryos

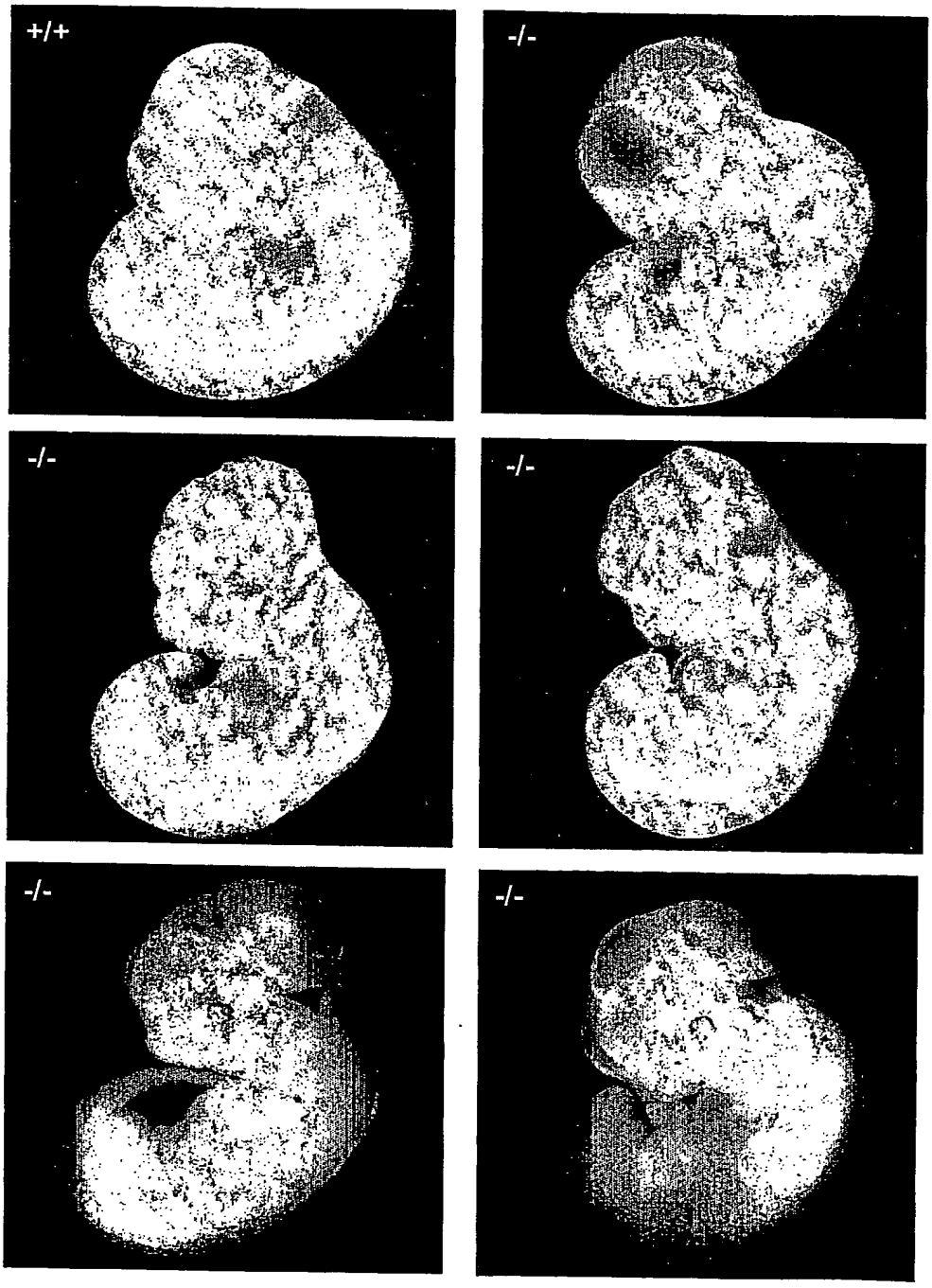
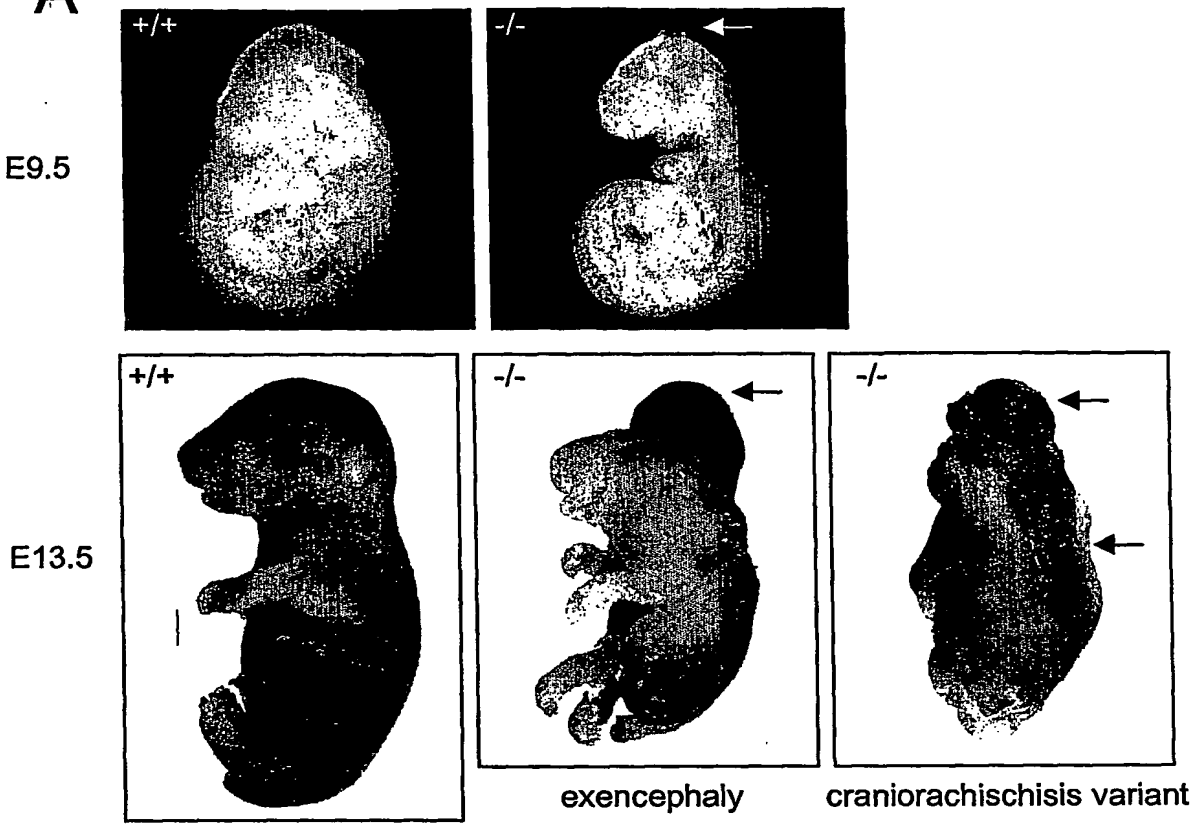


Figure 15

A **Embryos phenotype:**



B **Skeletal staining of embryo with exencephaly:**

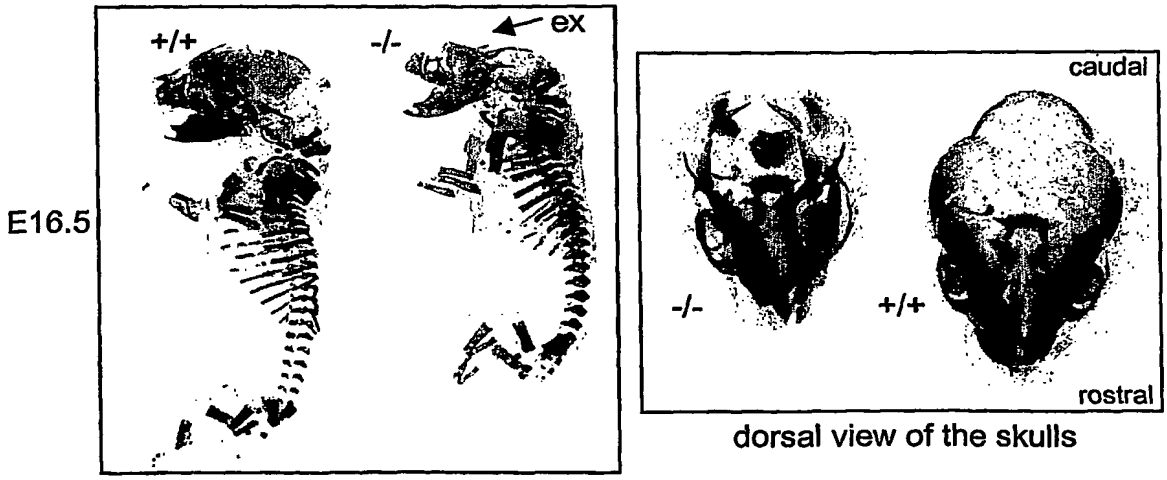
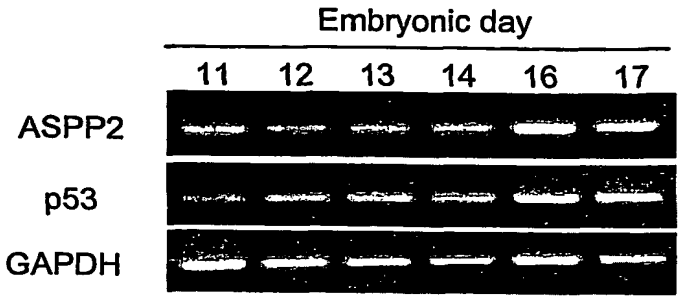
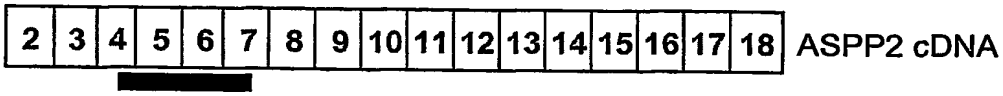


Figure 16

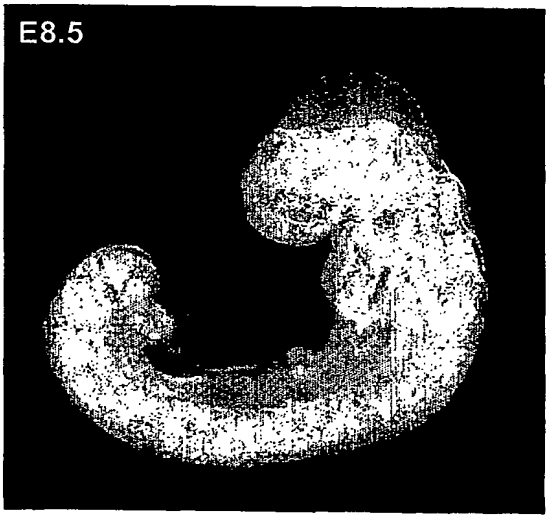
A **RT-PCR:**



B ***In situ* hybridization:**



probe
(40% homology with ASPP1)



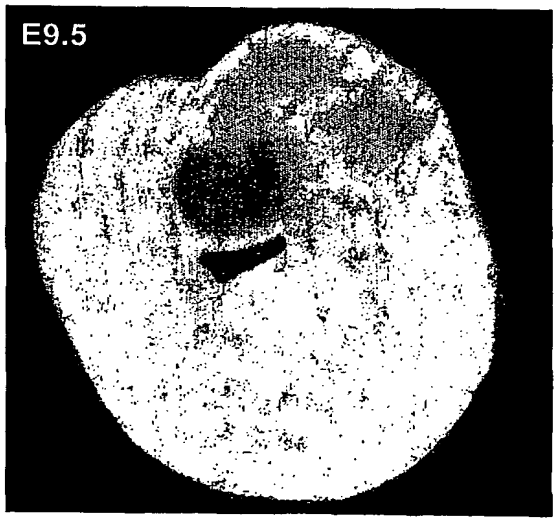
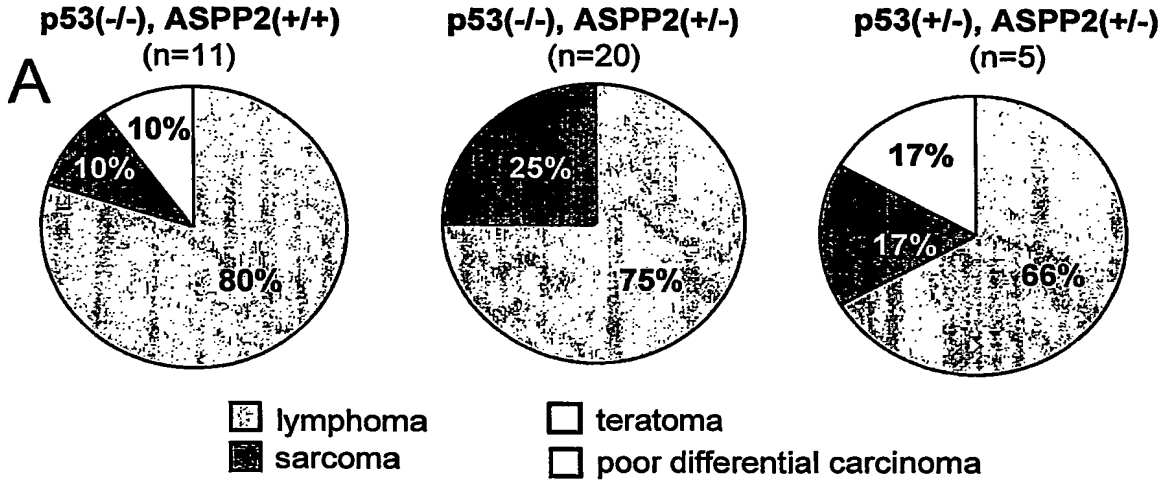


Figure 17


A
p53(-/-), ASPP2(+/+)
(n=11)
10%
10%
80%
p53(-/-), ASPP2(+/-)
(n=20)
25%
75%
p53(+/-), ASPP2(+/-)
(n=5)
17%
17%
66%
lymphoma
sarcoma
teratoma
poor differential carcinoma

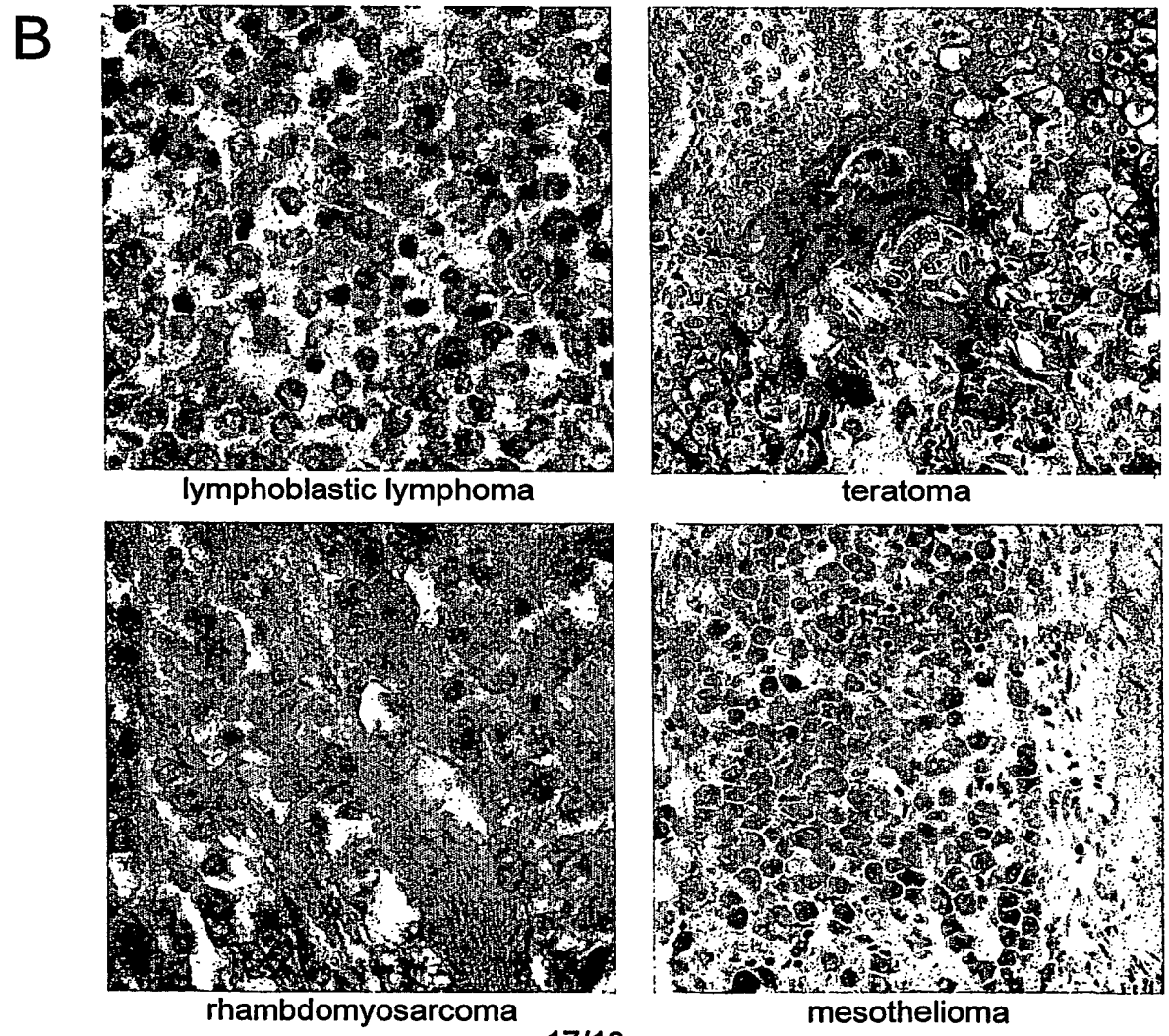
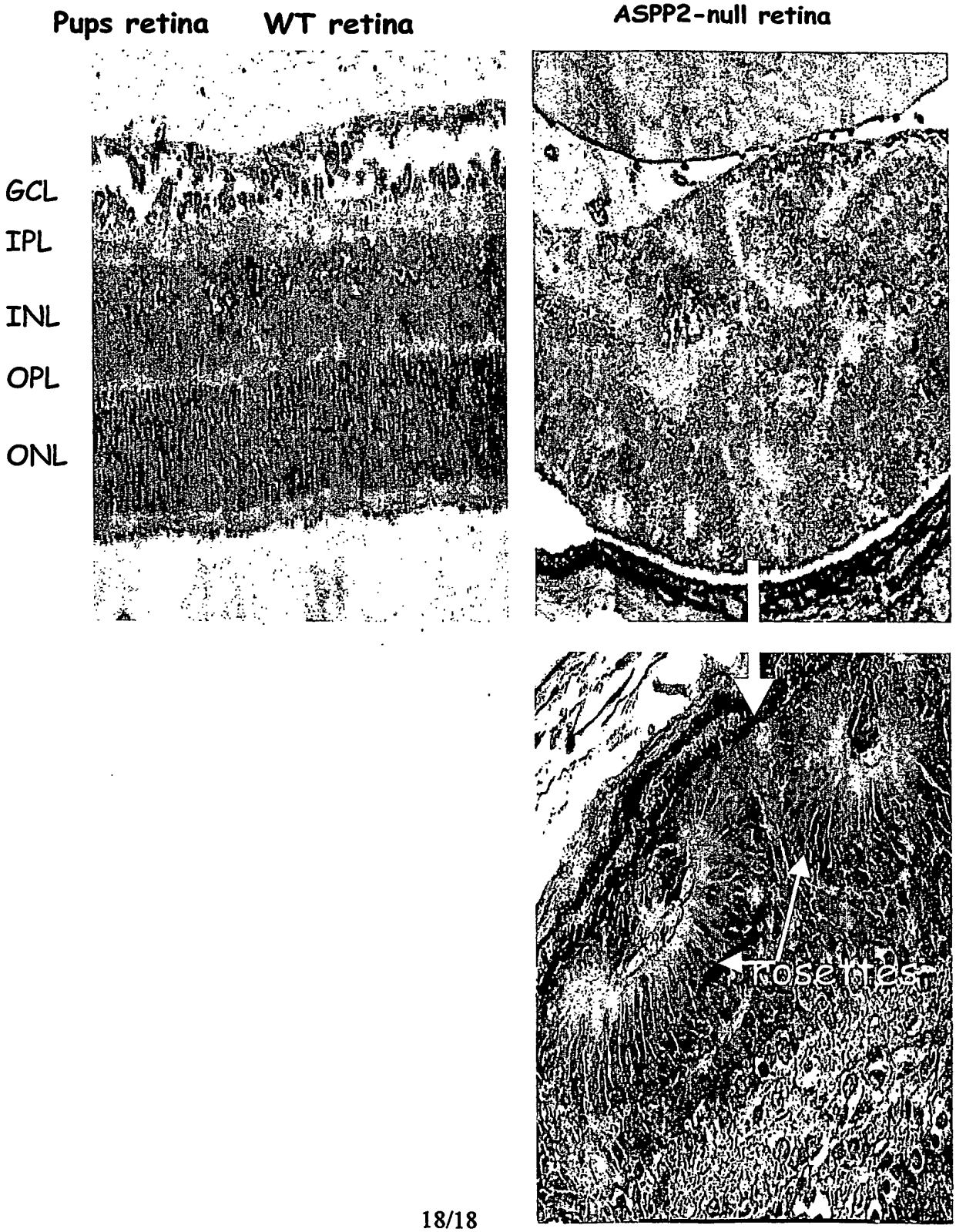

B
lymphoblastic lymphoma
teratoma
rhambdomyosarcoma
mesothelioma

Figure 18


Pups retina
WT retina
ASPP2-null retina
GCL
IPL
INL
OPL
ONL
rosettes